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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF

DE FLORA, ET AL. : EXAMINER: HOWARD V. OWENS, JR.

SERIAL NO: 09/125,022 : GROUP ART UNIT: 1623

FILED: NOVEMBER 24, 1998 :

FOR: PHARMACEUTICAL COMPOSITION ENABLING TO INHIBIT CANCER METASTASIS FORMATION CONTAINING N-ACETYL-CYSTEINE AND DOXORUBICIN

DECLARATION UNDER 37 C.F.R. ∋ 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313

SIR:

I, Silvio De Flora, hereby declare that:

1. I am Full Professor of Hygiene and Director of the Department of Health Sciences, formerly Institute of Hygiene and Preventive Medicine, University of Genoa, Genoa, Italy. My *curriculum vitae* which lists my accomplishments and publications is attached hereto.

2. I am one of the named inventors of the subject matter claimed in the above-described application.

3. I have reviewed the Office Action mailed July 15, 2003 and have been asked to provide information and comments regarding the Examiner's position that the subject matter set forth in Claims 13 through 17 of the above-identified application is anticipated by either

Freeman et al. ("Freeman"), *Toxicology and Applied Pharmacology*, Vol. 54, pp. 168-175 or Doroshow et al. ("Doroshow"), *J. Clinical Investigation*, Vol. 68, pp. 1053-64.

4. I am acquainted with the work of Freeman and Doroshow and have reviewed both the Freeman and Doroshow references relied on by the Examiner. I can state with certainty that the Freeman and Doroshow references do not anticipate the subject matter claimed in Claims 13 through 17 of the above-identified application.

5. Claims 13 through 17 are directed to a limited range of patients, *i.e.*, patients who have a tumor which is capable of metastasizing but which has not yet metastasized. Such tumors are normally solid tumors which, though "malignant," have not yet entered the metastasis stage.

6. The tumors used by Freeman and Doroshow are primary tumors which are not normally capable of metastasizing under the conditions utilized by Freeman and Doroshow. Freeman's work is based on a tumor model wherein the tumor was composed of a stock Ehrlich's ascites carcinoma which had been maintained in male mice for only 8 to 10 days. Ascites fluid from the mice was used to inoculate all the animals in Freeman's experiments. The mice were inoculated intraperitoneally. See Freeman, page 169, col. 1. The tumor cells in the ascites fluid used to inoculate the mice simply do not metastasize under such conditions. Accordingly, Freeman would not have achieved a synergistic prevention of metastasization as claimed in the above-identified patent application.

7. The Doroshow work also involves intraperitoneal implantation of mice but uses a different cell type, *i.e.*, P388 leukemia cells. The tumors, though malignant, do not metastasize in the mice containing the intraperitoneal malignancy. I note that the Doroshow reference, p. 1059, col. 2, advises that for this investigation, tumor cells, doxorubicin, NAC and saline were all present intraperitoneally to maximize the potential for any drug-drug interaction.

Accordingly, Doroshow's intraperitoneal experiments could not have exhibited prevention of metastasis because Doroshow's induced tumors were not tumors which under the circumstances were capable of metastasizing but had not yet metastasized as claimed in the above-identified application.

8. I have also noted that the Doroshow reference discusses the Freeman work at pages 1062 (col. 2) and 1063 (col. 1). Doroshow recognizes the work of Freeman and advances several possible mechanisms for the cardioprotective action of NAC and prolongation of life in doxorubicin-treated mice. Despite mentioning several possible mechanisms, Doroshow does not advance the hypothesis that the combination of NAC and doxorubicin synergistically prevented metastasis of the tumor.

9. In my opinion, it is technological error for the Examiner to rely on the work of Doroshow and Freeman as a basis for the "inherent" prevention of metastasis and consequent holding of anticipation. The tumor models used by Freeman and Doroshow are not the standard tumor models for testing metastasis. As explained in the article, De Flora et. al, *Synergism Between N-acetylcysteine and Doxorubicin in the Prevention of Tumorgenicity and Metastasis in Murine Models*, Int. J. Cancer, Vol. 67, pp. 842-848 (1996), the appropriate models for experimental metastasis assays constitute the injection of B16-F10 melanoma cells i.v. into (CD-1) BR nude mice or into the footpad of C57BL/6 mice.

10. As evidence that the P388 leukemia cells and Ehrlich's ascites carcinoma cells utilized in the work of Freeman and Doroshow do not suffice as models of metastasis. I include herewith the following technical articles which describe more appropriate models:

- Budzynski, "Lewis Lung Carcinoma in Mice as an ExperimentalTherapy Model I. The Growth Kinetics and the Effect of Tumor on Host," *Archivum Immunologiae et Therapiae Experimentalis,* 1982, 30, pp. 363-372.

I hereby declare that all statements made herein of my own knowledge are true and that all statement made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, Under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing theoron.

Date: 11/26/03

SILVIO DE FLORA

SILVIO DE FLORA, MD, PhD

FULL PROFESSOR OF HYGIENE AT THE SCHOOL OF MEDICINE

DIRECTOR OF THE DEPARTMENT OF HEALTH SCIENCES

UNIVERSITY OF GENOA, ITALY

SHORT CURRICULUM VITAE

- Born in Genoa (Italy) on 26 April 1942. Married, one son.

- Doctor in Medicine (6–year course) at the University of Genoa on 21 July 1966. "Libero docente" (=PhD) in Hygiene in session 1969.

- Career at the University of Genoa:
  - 1961-1966: Visiting undergraduate student at the Institute of Hygiene
  - 1966-1975: Assistant Professor at the Institute of Hygiene
  - 1975-present: Full Professor and Chairman of Hygiene at the School of Medicine
  - 1986-1998: Director of the Institute of Hygiene and Preventive Medicine
  - 1999-present: Director of the Department of Health Sciences (re–elected for the triennium 2002–2005).

- Member of the editorial boards of the following journals: Journal of Cellular Biochemistry (Chemoprevention Board), Mutation Research/Genetic Toxicology Testing, Mutation Research Letters, Mutagenesis, Toxicology Methods and Mechanisms, Tobacco Induced Diseases, European Journal of Epidemiology, Journal of Preventive Medicine and Hygiene, Igiene Moderna and Acta Oncologica.

- Editor of two special issues of Mutation Research, entitled "Role and Mechanisms of Inhibitors in Prevention of Mutation and Cancer" (Vol. 202, No. 2, 1988) and "Assessment of Antimutagenicity. End-Points and Systems" (Vol. 267, No. 2, 1992). Co-editor of a Plenum Press volume entitled "Antimutagenesis and Anticarcinogenesis Mechanisms III" (1993).

- Responsible for the preparation of documents for the United Nations Environment Program / World Health Organization (UNEP/WHO). Member of Working Groups of the International Agency for Research on Cancer (IARC) for the preparation of Monographs on the Evaluation of Carcinogenic Risks to Humans, Volumes 35 [Polynuclear Aromatic Compounds, 1985], 49 [Chromium, Nickel and Welding, 1990], and 58 [Berillium, Cadmium, Mercury and Glass Manufacture, 1993], and for the preparation of IARC Handbooks on Cancer Prevention [Preamble, IARC Scientific Publication No. 139, 1996], and Volumes 2 [Carotenoids, 1998] and 3 [Vitamin A, 1998].

- Member of a number of national and international scientific societies, among which EEMS, SIMA (Italian Society of Environmental Mutagenesis), and ISCaC (International Society of Cancer Chemoprevention), of which he was a founding member. In November 2000 he was appointed as a member of the Scientific Steering Committee of IAEMS (International Association of Environmental Mutagenesis Societies). In 2001 he declined an official nomination by EMS as IAEMS President for the quadriennium 2001–2005.

- He was awarded several prizes and honours, among which the Food, Nutrition, and Chronic Disease Fund awarded by the Michigan State University (East Lansing, MI) in May 2002. He was the second scientist, after Bruce Ames, to receive this honor.

- He undertook scientific collaborations, as documented by published articles, with 92 laboratories in the following countries: Bulgaria, Croatia, Finland, France, Germany, Greece, Italy, Japan, New Zealand, People's Republic of China, Russia, Sweden, The Netherlands, UK, and USA (see the list of collaborating laboratories in **Attachment A**).

- He is author, as to November 2003, of 359 full–length scientific publications, 218 of which published in journals quoted in the Science Citation Index (Journal Citation Reports, Institute for Scientific Information). The overall Impact Factor (JCR 2002) is 885.3. A selection of papers in the area of environmental mutagenesis, molecular epidemiology, and prevention of mutation–related diseases is reported in **Attachment B**.

- His research interests and areas of expertise covered two consecutive periods. From 1961 to 1975 the scientific activity focussed on medical and environmental virology. From 1975 onwards he has been interested in a variety of issues related to environmental mutagenesis and carcinogenesis, molecular epidemiology, and prevention of cancer and other mutation-related diseases (see details in the web site www.dissal.unige.it/NewFiles/mutag.html). The scientific publications deal with the following subjects (the numbers between brackets refer to the list reported in Attachment C):
  - Principles of epidemiology and prevention of mutation-related diseases (142, 148, 179, 199, 209, 251, 260, 292, 345)
  - Molecular biology approaches to cancer epidemiology and prevention (197, 211, 223, 244, 253, 280)
  - Development of animal models, also including use of mutant mice and transplacental exposures, for evaluating intermediate biomarkers and tumours after exposure to carcinogenic agents and complex mixtures (229, 252, 265, 306, 317, 321, 328, 331, 333, 350, 351)
  - Molecular and biochemical alterations and genetic polymorphisms in cancer, heart diseases, atherosclerosis, alopecia, glaucoma, and ageing (258, 274, 275, 286, 295, 312, 323, 324, 335, 338, 346, 347)

- Role and mechanisms of inhibitors of mutagenesis and carcinogenesis (173, 174, 182, 195, 214, 215, 226, 235, 246, 300, 311, 334)
- Inhibition of spontaneous and induced mutations and cancer in *in vitro* tests systems and animal models (227, 255, 257, 259, 283, 298, 315, 322, 330, 349)
- Chemopreventive effects and mechanisms of thiols, with special reference to *N*–acetylcysteine, in preclinical models (130, 140, 145, 149, 151, 157, 158, 167, 175, 183, 203, 207, 218, 219, 230, 234, 237, 239, 250, 267, 277, 279, 287, 290, 293, 301, 304, 336, 342, 348, 352, 359)
- Inhibition of angiogenesis, invasion and metastasis (273, 291, 302, 314, 319, 326, 337, 341)
- Chemoprevention clinical trials with *N*–acetylcysteine and oltipraz (288, 299, 332, 339)
- Lung carcinogenesis: effects of cigarette smoke, either active or passive, and of atmospheric pollution, mutagenic monitoring of air, pulmonary metabolism of mutagens in humans and animal models (127, 165, 172, 177, 186, 220, 222, 233, 261)
- Viral hepatitis B: biochemical changes and metabolism of chemical hepatocarcinogens, as related to the pathogenesis of primary hepatocellular carcinoma (137, 164, 178, 181, 198, 262, 276)
- Genotoxicity assessment of chemical compounds, with evaluation of structure–activity relationships, and of complex mixtures (cigarette smoke, polluted air particles), as related to their structure and carcinogenicity (101, 103, 104, 105, 106, 114, 116, 120, 125, 126, 131, 134, 138, 191, 256, 270)
- Metabolism of mutagens: biochemical mechanisms involved, interspecies and interindividual variability, role of detoxification as a threshold mechanism in carcinogenesis (75, 115, 117, 129, 141, 144, 156, 169, 264)
- Chromium: toxicology, mutagenicity, metabolism and carcinogenicity (72, 76, 77, 93, 100, 118, 122, 128, 135, 136, 147, 152, 153, 155, 160, 161, 162, 163, 166, 168, 184, 185, 188, 189, 196, 236, 268, 269, 294, 307, 325, 327, 343, 344)
- Oxidative mechanisms: genotoxicity of reactive oxygen species in bacterial test systems, and photoactivation of promutagens/procarcinogens (180, 187, 200, 247)
- Genotoxicity and carcinogenicity of UV light, sunlight, and artificial illumination systems, and their prevention (202, 212, 221, 228, 248, 263, 266, 297, 316, 320, 352)
- Fate of mutagens in the gastric environment: mutagenic monitoring, stability of mutagens, *in vitro* and *in vivo* nitrosation (89, 91, 97, 102, 107, 108, 112, 121, 123, 146, 159)
- Aquatic environment: mutagenic monitoring, chemical interactions, metabolism in aquatic organisms, monitoring of exposed organisms as related to pollution (81, 90, 113, 139, 193, 208, 216, 217, 240, 249, 271, 278, 281, 340).

- He has been involved as organizer, chairman and/or speaker in scientific congresses held worldwide (10 per year on an average).

- He is or has been the owner of a number of research grants released by the National Research Council (CNR, 5-year Targeted Projects, Strategic Projects, National Groups), the Italian Ministry of Education (also as national coordinator of a 7-year program), the

Italian Association for Cancer Research (AIRC), the Italian Ministry of University and Scientific-Technologic Research, the Italian Ministry for Foreign Affairs, the Italian Ministry of Labor and Social Previdence, the Ligurian Regional Agency, the University of Genoa, a variety of industrial sources, and the European Community (Bureau of Standards). In 1996 he was responsible for a sub-contract with the Johns Hopkins School of Hygiene and Public Health (Baltimore, MD). Since February 1996 he is Master Agreement Holder at the NCI Chemoprevention Branch on the subject "Preclinical evaluation of intermediate endpoints and their modulation by chemopreventive agents". In this position, competitively with 24 U.S. laboratories, he was awarded three consecutive contracts.

ATTACHMENT B

SILVIO DE FLORA, MD, PhD

FULL PROFESSOR OF HYGIENE AT THE SCHOOL OF MEDICINE

DIRECTOR OF THE DEPARTMENT OF HEALTH SCIENCES

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SELECTION OF PUBLICATIONS IN THE AREA OF ENVIRONMENTAL MUTAGENESIS, MOLECULAR EPIDEMIOLOGY AND PREVENTION OF MUTATION-RELATED DISEASES

Numbering of papers is drawn from the complete list of full-length articles

1977

72 Petrilli F.L. and De Flora S.: Toxicity and mutagenicity of hexavalent chromium on *Salmonella typhimurium*. *Appl. Environm. Microbiol.*, **33**, 805-809, 1977.

1978

75 De Flora S.: Metabolic deactivation of mutagens in the Salmonella/ microsome test. *Nature*, **271**, 455-456, 1978.

76 Petrilli F.L. and De Flora S.: Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat. Res.*, **54**, 139-147, 1978.

77 Petrilli F.L. and De Flora S.: Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. *Mutat. Res.*, **58**, 167-173, 1978.

1979

81 Petrilli F.L., De Renzi G.P., Palmerini Morelli M. and De Flora S.: Survey of the pollution in a coastal area of the Tyrrhenian Sea. Aerial photography, phisico-chemical and microbiological investigations and mutagenic monitoring. *Water Res.*, **13**, 895-904, 1979.

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86 De Flora S., Cajelli E. and Brambilla G.: Mutagenicity assay of an *Agaricus bisporus* extract. *IRCS Med. Science*, **7**, 185, 1979.

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89 De Flora S. and Boido V.: Effect of human gastric juice on the mutagenicity of chemicals. *Mutat. Res.*, **77**, 307-315, 1980.

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100 Petrilli F.L. and De Flora S.: Mutagenicity of chromium compounds. In *Chromate Symposium 80. Focus of a Standard*, Industrial Health Foundation, Pittsburg, Pennsylvania (U.S.A.), 1980, pp. 76-99.

1981

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103 Parodi S., De Flora S., Cavanna M., Pino A., Robbiano L., Bennicelli C. and Brambilla G.: DNA-damaging activity in vivo and bacterial mutagenicity of sixteen hydrazine derivatives as related quantitatively to their carcinogenicity. *Cancer Res.*, **41**, 1469-1482, 1981.

104 De Flora S. and Mugnoli A.: Relationships between mutagenic potency, reversion mechanism and metabolic behaviour within a class of chemicals (hydrazines). *Cancer Lett.*, **12**, 279-285, 1981.

105 De Flora S.: Study of 106 organic and inorganic compounds in the Salmonella/microsome test. *Carcinogenesis*, **2**, 283-298, 1981.

106 De Flora S.: A spiral test applied to bacterial mutagenesis assays. *Mutat. Res.*, **82**, 213-227, 1981.

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112 De Flora S., Zanacchi P., Camoirano A. and Bennicelli C.: Mutagenicity patterns resulting from the reaction of nitrite with ICR 170. *Mutat. Res.*, **103**, 13-17, 1982.

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114 Brambilla G., Cavanna M., Faggin P., Pino A., Robbiano L., Bennicelli C., Zanacchi P., Camoirano A. and De Flora S.: Genotoxic activity of five antidepressant hydrazines in a battery of in vivo and in vitro short-term tests. *J. Toxicol. Environ. Hlth.*, **9**, 287-303, 1982.

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120 De Flora S., Zanacchi P., Bennicelli C., Camoirano A., Cavanna M., Sciabà L., Cajelli E., Faggin P. and Brambilla G.: *In vivo* and *in vitro* genotoxicity of three antihypertensive hydrazine derivatives (hydralazine, dihydralazine and endralazine). *Environ. Mutagenesis*, **4**, 605-619, 1982.

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123 De Flora S. and Arillo A.: Mutagenic and DNA damaging activity in muscle of trout exposed in vivo to nitrite. *Cancer Lett.*, **20**, 147-155, 1983.

1984

125 Agnese G., Risso D. and De Flora S.: Statistical evaluation of inter- and intralaboratory variations of the Ames test, as related to the genetic stability of Salmonella tester strains. *Mutat. Res.*, **130**, 27-44, 1984.

126 De Flora S., Zanacchi P., Camoirano A., Bennicelli C. and Badolati G.: Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. *Mutat. Res.*, **133**, 161-198, 1984.

127 De Flora S., Bennicelli C., Zanacchi P., Camoirano A., Petruzzelli S. and Giuntini C.: Metabolic activation and deactivation of mutagens by preparations of human lung parenchyma and bronchial tree. *Mutat. Res.*, **139**, 9-14, 1984.

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137 De Flora S., Romano M., Basso C., Serra D., Astengo M. and Picciotto A.: Metabolic activation of hepatocarcinogens in chronic hepatitis B. *Mutat. Res.*, **144**, 213-219, 1985.

138 De Flora S., Russo P., Pala M., Fassina G.F., Zunino A.L., Bennicelli C., Zanacchi P., Camoirano A. and Parodi S.: Assay of phenacetin genotoxicity in vitro and in vivo test systems. *J. Toxicol. Environ. Hlth*, **16**, 355-377, 1985.

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146 De Flora S., Camoirano A., Basso C., Astengo M., Zanacchi P. and Bennicelli C.: Bacterial genotoxicity of nitrosated famotidine. *Mutagenesis*, **1**, 125-130, 1986.

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149 De Flora S., Romano M., Basso C., Bagnasco M., Cesarone C. F., Rossi G. A. and Morelli A.: Detoxifying activities in alveolar macrophages of rats treated with acetylcysteine, diethyl maleate and/or Aroclor. *Anticancer Res.*, **6**, 1009-1012, 1986.

151 De Flora S., Astengo M., Serra D. and Bennicelli C.: Inhibition of urethan-induced lung tumors in mice by dietary *N*-acetylcysteine. *Cancer Lett.*, **32**, 235-241, 1986.

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ATTACHMENT A

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Italian Institutions

University of Genoa, School of Medicine
- Cattedra di Chimica Propedeutica alla Biochimica
- Cattedra di Gastroenterologia, ISMI
- Cattedra di Nefrologia, ISMI
- Istituto di Chimica Biologica
- Istituto di Farmacologia
- Istituto di Medicina Legale
- Istituto di Oncologia
- Dipartimento di Oncologia Clinica e Sperimentale
- Istituto di Patologia Generale
- Istituto di Statistica Medica e Biometria
- Istituto di Dermatologia
- Istituto di Anatomia Umana
- Dipartimento di Scienze Biofisiche, Mediche e Odontostomatologiche, Università di Genova
- Dipartimento di Oncologia, Biologia e Genetica, Università di Genova
- Dipartimento di Scienze Neurologiche e della Visione, Università di Genova

University of Genoa, School of Biological Sciences
- Istituto di Chimica-Fisica
- Istituto di Fisiologia Generale
- Istituto di Zoologia
- Cattedra di Genetica

Other Italian Universities
- Dipartimento di Biologia Animale, Università di Padova
- Clinica Medica II, Università di Pisa
- Istituto di Anatomia Patologica, Università di Pisa
- Cattedra di Programmazione e Organizzazione dei Servizi Sanitari, Università La Sapienza di Roma
- Cattedra di Ecologia, Università di Urbino

-Istituto di Chimica Biologica, Università di Verona
-Dipartimento di Igiene e Medicina di Comunità, Università di Torino
-Istituto di Igiene e Medicina Preventiva, Università di Catania
-Istituto di Malattie Respiratorie, Università di Pavia
-Istituto di Scienze Farmacologiche, Università di Milano

Hospitals and Scientific Institutions
-Laboratorio di Biologia Molecolare, Istituto Nazionale per la Ricerca sul Cancro (IST), Genova
-Laboratorio di Mutagenesi - CSTA, Istituto Nazionale per la Ricerca sul Cancro (IST), Genova
-Laboratorio di Oncologia Sperimentale, Istituto Nazionale per la Ricerca sul Cancro (IST), Genova
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-Istituto G. Gaslini, Divisione di Pneumologia, Genova
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-Laboratorio di Analisi, Ospedale di Nervi, Genova
-Dipartimento di Anatomia Patologica, Ospedale Sampierdarena, Genova
-Centro di Biotecnologie Avanzate, Genova
-Ospedale SS. Pietro e Paolo, Borgosesia, Vercelli
-Fondazione Salvatore Maugeri, Pavia

Institutes of the National Research Council (CNR)
-Centro di Neurofisiologia Cerebrale, Genova
-Istituto per la Ricerca sulle Acque, Brugherio, Milano
-Istituto di Biochimica e Genetica Evoluzionistica, Pavia
-Istituto di Fisiologia Clinica, Pisa
-Istituto di Mutagenesi e Differenziamento, Pisa

Pharmaceutical Companies
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Other European Institutions

-International Agency for Research on Cancer (IARC), Lyon, France
-Department of Radiation Genetics and Chemical Mutagenesis, State University of Leiden, The Netherlands
-Department of Otolaryngology, Free University Hospital, Amsterdam, The Netherlands
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-Department of Physiology, University of Turku, Finland
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-Environmental Protection Agency, Seattle, Washington
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Institutions in Asia

-National Cancer Center Research Institute, Tokyo, Japan
-Department of Food and Nutrition, Ochanomizu University, Tokyo, Japan
-Faculty of Pharmaceutical Sciences, University of Okayama, Japan
-Department of Thoracic Surgery, Tokyo Medical University College, Tokyo, Japan
-Shanghai Cancer Institute, Shanghai, People's Republic of China
-Shanghai Medical University, Shanghai, People's Republic of China
-Qidong Liver Cancer Institute, Qidong, People's Republic of China

Institutions in Oceania

-Cancer Research Laboratory, University of Auckland School of Medicine, New Zealand